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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/739,264	10/29/96	MARSHALL	W

18M1/0710

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EXAMINER	
ZEMAN, M	
ART UNIT	PAPER NUMBER
1815	5

DATE MAILED: 07/10/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 2/7/97.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or ~~thirty days~~, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-23 is/are pending in the application.

Of the above, claim(s) 8-14 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-7 + 15-23 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

DETAILED ACTION

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1815.

Election/Restriction

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-7 and 15-23, drawn to methods of modulating the immune system of mammals, classified in class 424, subclass 278.1.

II. Claims 8-14, drawn to compositions of stress response factors, classified in class 424, subclass 282.1.

3. Inventions II and I are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the immune systems of mammals can be activated by the administration of bacteria or bacterial toxins as disclosed by Perdigon et al. 1990 J Food Production 53 (5) p 404-410.

4. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

5. During a telephone conversation with Heidi Nebel on 5/28/97 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-7 and 15-23. Affirmation of this election must be made by applicant in responding to this Office action. Claims 8-14 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(h).

Claim Objections

7. Claim 18 is objected to an am improper Markush-type claim. Acceptable wording for such a claim is "a delivery form selected from the group consisting of a, b, c, d, e, f , and g." The "and" should only be between the penultimate and ultimate members of the grouping. Language indicating intentional use ("for oral delivery") is not appropriate in a Markush grouping.

Claim Rejections - 35 USC § 112

8. Claims 15-23 are rejected as failing to define the invention in the manner required by 35 U.S.C. 112, second paragraph.

The claim(s) are narrative in form and replete with indefinite and functional or operational language. The steps of the method which make up the invention must be clearly and positively specified. The method must be organized and correlated in such a manner as to present a completely operative method. The claim(s) must be in *one sentence form only*. Note the format of the claims in the patent(s) cited.

The methods of claims 15-23 are vague and indefinite as they are lacking in positive active steps of the methods. Method claims should contain all of the steps necessary for carrying out the invention. For example, the method of claim 20 recites only one positive active step: administering bacteria. None of the rest of the material in this claim further point out necessary features of the method or components of the method.

It is suggested that applicant provide one independent claim drawn to a method of administering x to an animal (selected from p, q,, and r) for reasons a-d comprising administering x amount of y, in a form selected from e, f, g, and h. Further dependent claims may specify the individual animals, treatments, forms, reasons, or amounts, which, as an example, could be represented by: the method of claim Z wherein the factor is administered in animal feed. Any method claim that depends from another method claim must further limit that claim. Claims 15-

19 appear to be an attempt to follow this general outline. For claims 20-23 it is suggested that the method itself be mentioned in the preamble, "a method of protecting against bacterial infections.... comprising administration of x amount of y to an animal...", "a method of orally vaccinating an animal.... comprising administering x amount of y, and a killed pathogen...", "a method of augmenting animal feed... comprising the addition of x amount of y...."

9. Claims 5 and 15-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 does not further limit the invention of claim 1. The measurement of the amount of proteins collected by measuring their UV absorbencies at 220, 254, or 280 is a conventional step widely applied in protein studies. This does not further define the method of activating an immune response, nor does it further identify the proteins obtained by stressing bacteria.

The metes and bounds of the phrase "supernatant 10kDa" in claim 15 are not clear. There is no definition of this term as written in the specification. If applicant intends to claim a method of modulating the immune system of an animal comprising administering a supernatant of stressed bacteria as produced by the method of claim 1, amendments to that effect must be made. in the claim

In claim 16, to properly depend from claim 1, the following wording is suggested: The method of claim 1 wherein the modulation of the immune system is the protection of the animal against....."

Claims 17-21 recite the limitation "said composition" in reference to claim 1. There is insufficient antecedent basis for this limitation in the claim. Claim 1 does not contain the phrase "composition".

Claims 17, 19 and 21-23 recite the limitation "SRFs" in reference to claim 1. There is insufficient antecedent basis for this limitation in the claim. Claim 1 does not contain the word "SRFs" in the singular or plural, or the arbitrary units of those factors.

Claims 17, 19 and 21-23 recite the limitation "<10kDa" in reference to claim 1 (<20kDa in claim 23 also). There is insufficient antecedent basis for this limitation in the claim. Claim 1 does not contain the phrase "<10kDa".

Claim 20, depending from claim 1, does not administer the composition of claim 1. It appears to administer bacteria, instead of the product made by the method of claim 1.

The metes and bounds of claim 22 are indeterminable. No method steps are recited, and there is no link apparent between the language of claim 22 and claim 1. Claim 22 does not in any way seem related to the modulation of the immune system of an animal. The examiner is not able to determine the nature of the invention in this claim. This claim will *not* be further treated on the merits.

10. Claims 1-8, 15-21 and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not set forth in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The practice of this invention requires the use of bacteria which release certain low molecular weight proteins under certain conditions of stress. The pending claims do not disclose strains of bacteria which fulfill this requirement. As stated in the specification, page 4 "Therefore, not all strains of bacteria, even of the same specie, release levels of oligomers sufficient to protect animals against a subsequent bacterial infection." As the response of individual species of bacteria to various stressors is quite variable, and the number of characterized bacterial cell lines is enormous, the claims should include or refer to specific bacteria species or classes which are useful for the practice of the invention.

11. Claims 1-7, 16-21 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for activation of the immune system, does not reasonably provide enablement for the modulation of the immune system. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The specification, as filed, only refers to the *activation* of an immune response. Modulation implies repression or depression could also occur through the same method. The specification as filed does not disclose the repression or depression of an immune response.

12. Claims 15, 17, 19-21 and 23 will be interpreted in the following way for the purposes of the application of prior art in this examination:

Claim 15 will be examined as a method of activating the immune system of an animal comprising administering proteins released into the supernatant of stressed bacteria, wherein the molecular weights of the proteins are less than 10kDa.

Claim 17 will be examined as the method of claim 1 wherein the animal is poultry or livestock, and 1000 to 50,000 arbitrary units of the proteins released into the supernatant of stressed bacteria are administered.

Claim 19 will be examined as the method of claim 1 wherein the animal is a human, and 1000 to 50,000 arbitrary units of the proteins released into the supernatant of stressed bacteria are administered.

Claim 20 will be examined as the method of claim 1 wherein the animal is poultry or livestock, and bacteria are administered.

Claim 21 will be examined as the method of claim 1 wherein the proteins released into the supernatant of stressed bacteria in combination with a killed pathogen are administered to the animal.

Claim 23 will be examined as the method of claim 1 wherein the proteins released into the supernatant of stressed bacteria are administered to the animal in animal feed.

These interpretations are for the purposes of applying the prior art. This does *not* release the burden upon Applicant to respond to the above rejections.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-5, 6, 7, 15, 17 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Vuyst.

Claims 1-5 and 7 are drawn to methods of modulating the immune system of an animal through the administration of the supernatant from stressed bacteria to the animal. Specific stresses include reducing the bioavailability of nutrients, crowding the bacteria, altering the pH, and placing bacteria in a non-nutritive solution. Claim 6 requires the removal of proteins larger than 10kD. Claims 15 and 17 are being examined as a method of modulating the immune system of an animal by administering a low molecular weight fraction of a supernatant derived from

stressed bacteria. Claim 23 is drawn to the administration of the supernatant of stressed bacteria to animals in animal feed.

De Vuyst (De Vuyst et al. 1996 142 p 817-827) disclose methods of producing low molecular weight proteins from bacteria by subjecting them to a number of stresses. These stresses include: a change in temperature, a change in pH, a change in biomass (crowding or decreasing the amount of media), and adding toxins such as ethanol. Subjecting the lactic acid bacteria to any of these stressors results in the release of low molecular weight monomers of bacteriocin (approx 6kD or less) that oligomerize to be about 30kD. De Vuyst removes components larger than the individual bacteriocin, approximately 6kD. These bacteriocins are able to kill or harm other bacterial species. De Vuyst suggests, but does not explicitly teach, the use of the bacteriocins as food additives. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have followed the suggestion of De Vuyst and administer the low molecular weight proteins resulting from the stressing of bacteria to animals, as the bacteriocins can act to kill or render harmless other strains of bacteria.

15. Claims 16, 18 and 19 rejected under 35 U.S.C. 103(a) as being unpatentable over De Vuyst as applied to claims 1-5, 15, 17 and 23 above, further in view of Nanji.

Claims 16, 18, and 19 are drawn to protecting poultry, livestock, or humans from shock, allergic reactions or immune suppression by the method of claim 1.

De Vuyst discloses methods for producing the low molecular weight proteins from stressed bacteria, and suggests adding those proteins to food. Nanji (US Patent 5,413,785)

discloses the administrations of lactic acid bacteria to humans, livestock, and other animals for protection against endotoxin-mediated shock. The bacteria can be administered a variety of ways. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the routes of administration and selected hosts to be immunized as set forth by Nanji for the administration of the low molecular weight stress proteins disclosed by De Vuyst. Nanji indicates that lactic acid bacteria is able to protect against enterotoxin mediated shock, and De Vuyst disclosed low molecular weight proteins released from lactic acid bacteria which could modulate the immune system.

16. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Perdigon.

Claim 20 is being examined as a method of modulating the immune system of an animal (poultry or livestock) by the administration of bacteria.

Perdigon (Perdigon et al. 1990 J Food Prot. 53 (5) p 404-410) discloses the feeding of lactic acid bacteria to mice, and this treatment results in an increased immunity to enteropathogens. Perdigon does not explicitly disclose the use of these products in poultry or livestock, but Perdigon does discuss the use of lactic acid bacteria in various food products such that it can modulate the immune system of the animal ingesting it.

17. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Farr.

Farr (US Patent 3,953,609) discloses modulation of the immune system of livestock by the administration of lactic acid bacteria. Animals fed these bacteria were protected against mastitis.

18. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over De Vuyst as applied to claims 1-5, 15, 17 and 23 above, further in view of Perdigon.

Claim 21 is being examined as a method of modulating the immune system of an animal by administering the low molecular weight stress proteins as an adjuvant. Perdigon (supra) discloses the use of lactic acid bacteria and the proteins produced therein as adjuvants in the generation of protection from enteropathogens. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the low molecular weight proteins disclosed by De Vuyst as adjuvants for the induction of an immune response to another coadministered pathogen. Perdigon discusses the use of lactic acid bacteria as adjuvants for enteropathogens, and an increased immune response was disclosed. De Vuyst disclosed that proteins produced by lactic acid bacteria have an immunomodulatory effect.

19. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over De Vuyst as applied to claims 1-5, 15, 17 and 23 above, further in view of Emery.

Emery (US Patent 5,538,733) discloses the use of a bacteriocin, such as the one disclosed by De Vuyst, in combination with a wide variety of other pathogens, attenuated, killed, or subunits thereof. Emery notes bacteriocin is a effective immunogen, as the administration of bacteriocin results in a good immune response, that can prevent reinfection. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the low molecular weight proteins disclosed by De Vuyst in combination with another pathogen. One would have expected an active immune response to have been generated as set forth in Emery.

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (703) 305-7133. The examiner can be reached between the hours of 8:00 am and 5:30 pm Monday through Thursday, and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marian Knode, can be reached on (703) 308-4311.

The fax number for this Art Unit is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Marian C. Knode

mkz
June 24, 1997

MARIAN C. KNODE
SUPERVISORY PATENT EXAMINER
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